

**REMARKS*****Status of Claims***

Claims 80-83 and 87-93 are currently pending. Claim 80 and 91-93 are currently amended. Support for the amended and added claims is found throughout the specification as originally filed, *inter alia*, at the following: page 2, lines 6-7, Figure 11, and page 55, lines 19-21. Accordingly, Applicants submit that no new matter is introduced into the specification by way of the present amendments pursuant to 35 U.S.C. § 132. Applicants respectfully request entry of the amendments, reconsideration of the rejections, and allowance of the pending claims.

***Objections to the Specification***

The title of the application has been changed to: Methods of Treating Disorders of the Eye. Applicants respectfully submit that this amendment obviates the Examiner's objection. Withdrawal of this objection is requested.

***35 U.S.C. § 103(a): Yan and Milbrandt***

Claims 80-83 and 87-90 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Yan *et al.* (U.S. Patent No. 5,641,749; "Yan") in view of Milbrandt *et al.* (U.S. Patent No. 6,284,540; "Milbrandt"). Applicant respectfully request withdrawal of this rejection for the reasons provided herein.

The Office Action fails to set forth a rationale as to why a person of ordinary skill in the art would expect two structurally and functionally distinct polypeptides operating through distinct receptor pathways to be obvious substitutions for one another. Applicants respectfully maintain that ARTN/NBN and GDNF are different proteins that possess different structure and different biological activity. As is summarized in the specification at page 2, lines 6-7, ARTN/NBN exhibits high affinity for GDNF family receptor  $\alpha 3$  (GFR $\alpha$ -3). GDNF, on the other hand, does not bind to GFR $\alpha$ -3, but rather

binds to GDNF family receptor  $\alpha 1$  (GFR $\alpha$ -1). The specification at page 55, lines 19-21 highlights the functional difference between Neublastin and GDNF as follows:

[N]eublastin binds to GFR $\alpha$ -3 but not to GFR $\alpha$ -1. This behavior clearly distinguishes neublastin from GDNF; as shown in FIG. 11, GDNF binds to GFR $\alpha$ -1 but not to GFR $\alpha$ -3.

The Examiner alleges that Milbrandt teaches that ARTN/NBN can also bind and activate GFR $\alpha$ -1, and “[t]hus, it would have been obvious to substitute GDNF in the method of Yan.<sup>1/</sup> However, it is not a fact that ARTN/NBN can also bind and activate GFR $\alpha$ -1. Indeed, several groups have reported that ARTN/NBN does not bind and activate GFR $\alpha$ -1 in a physiologically significant manner. For example, Figure 11 of WO 2000/01815 reports a comparison of ARTN/NBN and GDNF binding to GFR $\alpha$ -1 and GFR $\alpha$ -3 receptors, wherein it is clear that GDNF acts on GFR $\alpha$ -1 and NBN acts on GFR $\alpha$ -3 and that there is no cross-talk.

The data presented in Figure 11 of WO 2000/01815 is supported by Rakowicz<sup>2/</sup>, which specifically teaches that GDNF is the exclusive physiological ligand for GFR $\alpha$ -1. It is important to note that Milbrandt himself is co-author of this report and that ARTN/NBN was also tested and compared to GDNF. Specifically, Rakowicz at page 3958, left column, last paragraph provides as follows:

“To examine the physiological importance of GFR $\alpha$ -1 for GDNF-dependent motor neuron (MN) survival, slice cultures were prepared from *GFR $\alpha$ -1<sup>-/-</sup>* mice and cultured in the presence of GDNF or no trophic factor. The survival response to GDNF was completely abolished in *GFR $\alpha$ -1<sup>-/-</sup>* neurons (Fig. 7C). Thus, the trophic effect of GDNF on MNs is completely mediated by the *GFR $\alpha$ -1* co-receptor. Furthermore, despite *in vitro* evidence in cell lines of potential cross talk between different GFL members and their respective receptors [...], in this paradigm only GDNF induces a significant MN survival signal through *GFR $\alpha$ -1*. The absence of a detrimental effect of the other GFLs when coadministered with GDNF suggests that they do not compete with GDNF for receptor binding.”

In addition, on page 3960 of Rakowicz, Figure 7 (as mentioned in the above cited text) provides an overview of these results clearly showing that GDNF is the exclusive

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<sup>1/</sup> See Office Action at page 4, lines 14-16

<sup>2/</sup> *J Neurosci.* 2002 May 15;22(10):3953-62.

physiological ligand for GFR $\alpha$ -1 and that none of the other GDNF-family ligands can promote survival of the motor neurons; and that none of them compete with GDNF for binding to GFR $\alpha$ -1. On the same page, right column the paragraph headline states that “*GDNF is the exclusive physiological ligand for GFR $\alpha$ -1*”, and the last sentence in that paragraph states: “Thus not only were none of these factors in isolation survival-promoting for MNs, but they also showed no evidence of competition with GDNF for receptor binding, supporting a model of a physiologically exclusive interaction between GDNF and GFR $\alpha$ -1”.

A subsequent study by Carmillo<sup>3/</sup> confirms the findings of Rakowicz. For example, Figures 1-3 of Carmillo shows that GFR $\alpha$ -1 is highly selective for GDNF as compared to ARTN/NBN. Based on these results, Carmillo concludes that “GFR $\alpha$ -1 is not likely to be a functional coreceptor for [ARTN/NBN] *in vivo*.”<sup>4/</sup>

Accordingly, the teachings of Milbrandt (US 6,284,549) have been demonstrated as incorrect, or in the least, as not physiologically relevant. Indeed, the evidence of record indicates that Milbrandt has himself admitted that GDNF is the exclusive physiological ligand for GFR $\alpha$ -1. Consequently, Applicants maintain that GDNF and ARTN/NBN are structurally distinct and that the skilled artisan cannot extrapolate the biological activity of GDNF to ARTN/NBN.

As such, ARTN/NBN is structurally and functionally distinct from GDNF. Accordingly, this does not create a scenario where a person of ordinary skill in the art could easily substitute one element of the prior art for another. The Office Action relies on the general teachings in Yan and Milbrandt that identify ARTN/NBN and GDNF generally as neurotrophic growth factors. The Office Action, however, fails to consider the distinct modes of action by which these growth factors elicit their biological effect. That ARTN/NBN and GDNF are generally known in the art as neurotrophic growth

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<sup>3/</sup> Biochemistry. 2005 Feb 22;44(7):2545-54.

<sup>4/</sup> Id. at Abstract.

factors can not support a conclusion that the claims would have been obvious to one of ordinary skill in the art.

Furthermore, as is explained by the Federal Circuit, the motivation to combine is part of the discussion in determining the scope and content of the prior art.<sup>5</sup> Thus, where all claim limitations are found in a number of references, the factfinder must determine "[w]hat the prior art teaches... and whether it motivates a combination of teachings from different references".<sup>6</sup> Here, Milbrandt fails to disclose a method of using ARTN/NBN for the treatment of an eye disorder such as macular degeneration, retinitis pigmentosa, or glaucoma. Nowhere in Milbrandt is it even taught that ARTN/NBN is expressed in the retina. Thus, there is no suggestion in Milbrandt that ARTN/NBN may be used in the manner now claimed. Yan discloses the use of GDNF, which as above, is a structurally different protein and produces its biological effect through a different biological mechanism. A person of ordinary skill in the art would appreciate these differences and would not have been motivated to combine the teachings of Yan and Milbrandt to arrive at the present invention. Because of the structural and functional differences between ARTN/NBN and GDNF, a person of ordinary skill in the art would not "be able to fit the teachings of multiple patents together like pieces of a puzzle."<sup>7</sup>

In view of the above, Applicants respectfully submit that the Office Action fails to set forth a *prima facie* case of obviousness. Accordingly, Applicants request withdrawal of this rejection.

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<sup>5</sup> DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co., 464 F.3d 1356, 1360, 80 USPQ2d 1641, 1645 (Fed. Cir. 2006); *citing* SIBIA Neurosciences, Inc. v. Cadus Pharma, Corp., 225 F.3d 1349, 1356 (Fed. Cir. 2000).

<sup>6</sup> *Id.* *citing* In re Fulton, 391 F.3d 1195, 1199-1200 (Fed. Cir. 2004).

<sup>7</sup> KSR, 82 USPQ2d at 1397.

**35 U.S.C. § 103(a): Yan, Milbrandt, and Hammang**

Claims 80-83 and 87-93 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Yan *et al.* (U.S. Patent No. 5,641,749; “Yan”) in view of Milbrandt *et al.* (U.S. Patent No. 6,284,540; “Milbrandt”), as applied to claims 80-83, 87-90, and 93 above, and further in view of Hammang *et al.* (U.S. Patent No. 6,299,895; “Hammang”). Applicant respectfully request withdrawal of this rejection for the reasons provided herein.

As stated above, ARTN/NBN is structurally and functionally distinct from GDNF. Accordingly, this does not create a scenario where a person of ordinary skill in the art could easily substitute one element of the prior art for another. The Office Action fails to set forth a rationale as to why a person of ordinary skill in the art would expect two structurally and functionally distinct polypeptides operating through distinct receptor pathways to be obvious substitutions for one another. That ARTN/NBN and GDNF are generally known in the art as neurotrophic growth factors can not support a conclusion that the claims would have been obvious to one of ordinary skill in the art.

Further, as stated above, Milbrandt fails to disclose a method of using ARTN/NBN for the treatment of an eye disorder such as macular degeneration, retinitis pigmentosa, or glaucoma. Yan discloses the use of GDNF, which as above, is a structurally different protein and produces its biological effect through a different biological mechanism. A person of ordinary skill in the art would appreciate these differences and would not have been motivated to combine the teachings of Yan and Milbrandt to arrive at the present invention.

Hammang is relied upon by the Examiner for its teaching of GDNF in the treatment of macular degeneration and retinitis pigmentosa as recited in claims 80, 91, and 92. Hammang does not teach NBN, nor does Hammang teach or suggest the use of NBN in the treatment of macular degeneration or retinitis pigmentosa. Accordingly, Hammang does not cure the above noted deficiencies of Yan and Milbrandt. Further, Applicants respectfully maintain that the Office Action fails to set forth a rationale as to

why a person of ordinary skill in the art would expect two structurally and functionally distinct polypeptides operating through distinct receptor pathways to be obvious substitutions for one another. Withdrawal of this rejection is respectfully requested.

***Reply to Claim Rejections Under 35 U.S.C. § 112, First ¶, Enablement***

Claims 80-83 and 87-93 are rejected under 35 U.S.C. § 112, first ¶, because the specification, while being enabled for a method of treating photoreceptor loss in the retina of patents afflicted with macular degeneration, retinitis pigmentosa, or glaucoma, comprising administering to the eye of the patient a cell line expressing a Neublastin polypeptide comprising the amino acid sequence of SEQ ID NO: 9, 10, 11, or 12, allegedly does not reasonably provide enablement for amino acid sequence of at least 95% sequence identity with SEQ ID NO: 12 or any amino acid sequences of SEQ ID NO: 9-12.

Applicants respectfully disagree with this assessment. First, the specification provides for multiple assays that may be used by one of skill in the art to assess whether a an amino acid sequence at least 95% homologous to SEQ ID NO: 12 would possess neurotrophic activity. Second, the analysis set forth in the Office Action appears only to consider those amino acid sequences that were elected in the present application, SEQ ID NOs: 9, 10, 11, and 12. The specification sets forth several protein sequences that share a varying degree of sequence identity with SEQ ID NO: 12 that possess the desired activity. For example, SEQ ID NO: 16 shares 88.5% identity in a 113 residue overlap with SEQ ID NO: 12; SEQ ID NO: 2 shares 91.1% identity in a 112 residue overlap with SEQ ID NO: 12; and SEQ ID NO: 4 shares 97.3% identity in a 113 residue overlap with SEQ ID NO: 12. These alignments were executed using the SIM - Alignment Tool for protein sequences available at <http://expasy.org/tools/sim-prot.html> and are provided below for the convenience of the Examiner.

Results of SIM with:  
Sequence 1: SeqIDNO:12, (113 residues)  
Sequence 2: SeqIDNO:2, (200 residues)  
using the parameters:  
Comparison matrix: BLOSUM62  
Number of alignments computed: 20

Gap open penalty: 12  
Gap extension penalty: 4

91.1% identity in 112 residues overlap; Score: 531.0; Gap frequency: 0.9%

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SeqIDNO:12      2  GGPGRSARAAGARGCRLRSQVLPVRLGLGHRSDLVRFRCGSGCRRARSPHDLASL
SeqIDNO:2,      90  GGRAARSGSGGA--GCRLRSQVLPVRLGLGHRSDLVRFRCCTGSCPRARSPHDLASL
                ** *      * * * * *
SeqIDNO:12      62  LGAGALRPPPGSRPVSQPCCRPTRYEAVSFMDVNSTWRTVDRLSATACGCLG
SeqIDNO:2,      149 LGAGALRPPPGSRPVSQPCCRPTRYEAVSFMDVNSTWRTVDRLSATACGCLG
                * * * * *
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Results of SIM with:  
Sequence 1: SeqIDNO:12, (113 residues)  
Sequence 2: SeqIDNO:4, (237 residues)  
using the parameters:  
Comparison matrix: BLOSUM62  
Number of alignments computed: 20  
Gap open penalty: 12  
Gap extension penalty: 4

97.3% identity in 113 residues overlap; Score: 588.0; Gap frequency: 0.0%

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SeqIDNO:12      1  AGGPGRSARAAGARGCRLRSQVLPVRLGLGHRSDLVRFRCGSGCRRARSPHDLASL
SeqIDNO:4,      125 AGGPGINRARAAGARGCRLRSQVLPVRLGLGHRSDLVRFRCGSGCRRARSPHDLASL
                *****
SeqIDNO:12      61  LLGAGALRPPPGSRPVSQPCCRPTRYEAVSFMDVNSTWRTVDRLSATACGCLG
SeqIDNO:4,      185 LLGAGALRPPPGSRPVSQPCCRPTRYEAVSFMDVNSTWRTVDRLSATACGCLG
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Results of SIM with:  
Sequence 1: SeqIDNO:12, (113 residues)  
Sequence 2: SeqIDNO:16, (224 residues)  
using the parameters:  
Comparison matrix: BLOSUM62  
Number of alignments computed: 20  
Gap open penalty: 12  
Gap extension penalty: 4

88.5% identity in 113 residues overlap; Score: 528.0; Gap frequency: 0.0%

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SeqIDNO:12      1  AGGPGRSARAAGARGCRLRSQVLPVRLGLGHRSDLVRFRCGSGCRRARSPHDLASL
SeqIDNO:16      112 AGTRSSRARTTDARGCRLRSQVLPVRLGLGHRSDLVRFRCGSGCRRARSPHDLASL
                ** * * * * *
SeqIDNO:12      61  LLGAGALRPPPGSRPVSQPCCRPTRYEAVSFMDVNSTWRTVDRLSATACGCLG
SeqIDNO:16      172 LLGAGALRPPPGSRPVSQPCCRPTRYEAVSFMDVNSTWRTVDRLSATACGCLG
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Further, Applicants respectfully submit that the Examiner has not set forth any evidence to support the conclusion that the Neublabin polypeptide sequences as claimed would not possess neurotrophic activity. In order to establish a *prima facie* case of non-enablement, the Examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure. See In re

Wright, 999 F.2d 1557, 1561-562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). A disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, *unless* there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. See In re Marzocchi, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). As stated by the court, it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure.

The threshold step in resolving this issue is to determine whether the Examiner has met his burden of proof by advancing acceptable reasoning inconsistent with enablement. In re Morehouse, 545 F.2d 162, 165, 192 USPQ 29, 32 (CCPA 1976). Further, even a broad allegation that the disclosure is speculative, coupled with a recitation of various difficulties which might be encountered in practice, is not sufficient basis for requiring proof of operability. In re Chilowsky, 229 F.2d 457, 462, 108 USPQ 321, 325 (CCPA 1956).

In the present case, Applicants respectfully submit that the Examiner has not provided acceptable evidence that the claimed invention is inconsistent with enablement. At best, the Examiner has made broad allegations that the disclosure is speculative and recited various difficulties that might be encountered in practice of the invention. For example, the rejection on page 9 states that the specification “fails to provide sufficient guidance as to whether all Neublabin polypeptides including fragments, variants, and derivatives could be used in the claimed method since a single amino acid change could abolish the binding of a molecule.” The Office Action goes on the cite Burgess to support the above argument. Burgess, however, does not disclose a method of treating a



disorder of the eye comprising administering to an individual in need thereof a cell line expressing a NBN polypeptide, nor NBN binding of GFR $\alpha$ -3, nor treatment of macular degeneration, retinitis pigmentosa, and/or glaucoma. Hence, Burgess can not be relied upon for determining loss of neurotrophic activity by altering single amino acids in NBN113. Furthermore, as stated above, the specification provides for multiple assays that may be used by one of skill in the art to assess whether an amino acid sequence at least 95% identical to SEQ ID NO: 12 would have the desired activity. As it is stated in claim 80, the claimed polypeptides (which is at least 95% identical to SEQ ID NO. 12) possess neurotrophic activity, and thus, the arguments by the examiner that altering an amino acid may alter the specificity and binding affinity of a certain variant is irrelevant. Taken together, the Office Action has not provided sufficient evidentiary basis for requiring proof of enablement and a shifting of the burden of proof to appellant.

In this regard, the following passage from PPG Indus., Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1564, 37 USPQ2d 1618, 1623 (Fed. Cir. 1996) is instructive.

In unpredictable art areas, this court has refused to find broad generic claims enabled by specifications that demonstrate the enablement of only one or a few embodiments and do not demonstrate with reasonable specificity how to make and use other potential embodiments across the full scope of the claim. See, e.g., In re Goodman, 11 F.3d 1046, 1050-52, 29 USPQ2d 2010, 2013-15 (Fed. Cir. 1993); Amgen, Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200, 1212-14, 18 USPQ2d 1016, 1026-28 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991); In re Vaeck, 947 F.2d at 496, 20 USPQ2d at 1445. Enablement is lacking in those cases, the court has explained, because the undescribed embodiments cannot be made, based on the disclosure in the specification, without undue experimentation. But the question of undue experimentation is a matter of degree. The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation “must not be unduly extensive.” Atlas Powder Co., v. E.I. DuPont De Nemours & Co., 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984). The Patent and Trademark Office Board of Appeals summarized the point well when it stated:

The test is not merely quantitative, since a *considerable amount of experimentation is permissible*, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed. Ex parte Jackson, 217 USPQ 804, 807 (1982).

In the present case, even if a considerable amount of experimentation is required to determine those Neublastin polypeptides that possess neurotrophic activity, such experimentation is routine to those of ordinary skill in the relevant art.

***Reply to Claim Rejections Under 35 U.S.C. § 112, First ¶, Written Description***

Claims 80-83 and 87-93 are also rejected under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement. Applicants respectfully submit that the entire scope of the claimed subject matter also meets the written description requirement of 35 U.S.C. 112, ¶ 1. Example 10 of the Written Description Guidelines Revision 1<sup>8/</sup> provides useful guidance in determining what scope of claims would be allowable with respect to the written description requirement. Example 10 considers the following hypothetical claim:

Claim 2. An isolated variant of a protein comprising the amino acid sequence shown in SEQ ID NO: 3, wherein the variant comprises an amino acid sequence that is at least 95% identical to SEQ ID NO: 3.

The example explains that because the specification adequately describes proteins comprising the amino acid sequence of SEQ ID NO: 3, the specification also adequately describes proteins that are at least 95% identical to SEQ ID NO: 3. That is because all of the species within the genus share a significant degree of partial structure (*i.e.*, at least 95% of SEQ ID NO: 3). The example also explains that the claimed variants can have amino acid substitutions, deletions, insertions, or additions, as compared to SEQ ID NO: 3. This is because those skilled in the art would expect members of the genus to have properties similar to those of SEQ ID NO: 3, because of the high degree of structural similarity. Specifically, the PTO concludes that the hypothetical claim provides adequate written description for the following reasons:

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<sup>8/</sup> Revision of March 25, 2008 available at <http://www.uspto.gov/web/menu/written.pdf>.

The specification adequately describes proteins comprising the amino acid sequence of SEQ ID NO: 3 (see the analysis of claim 1). All of the proteins within the scope of claim 2 share at least 95% of the amino acid sequence of SEQ ID NO: 3; therefore, the specification describes 95% of the structure that defines the proteins within the claimed genus. All of the species within the genus share a significant degree of partial structure (i.e., at least 95% of SEQ ID NO: 3). The claimed variants can have amino acid substitutions, deletions, insertions, or additions, as compared to SEQ ID NO: 3. The specification does not provide an actual reduction to practice of any variants of the protein of SEQ ID NO: 3. The specification does not describe the complete structure or physical or chemical properties of any variants of SEQ ID NO: 3, although those skilled in the art would expect members of the genus to have properties similar to those of SEQ ID NO: 3, because of the high degree of structural similarity. In view of the disclosure of SEQ ID NO: 3, those skilled in the art could readily envision all of the amino acid sequences that are 95% identical to SEQ ID NO: 3. Those skilled in the art could recognize amino acid sequences that are 95% identical to SEQ ID NO: 3 by comparing a given sequence to SEQ ID NO: 3. The presence of an amino acid sequence that is at least 95% identical to SEQ ID NO: 3 is a structural feature of each of the proteins within the claimed genus.

The level of skill and knowledge in the art is such that one of ordinary skill would be able to make and identify variants having 95% identity to SEQ ID NO: 3 routinely.

Thus, those skilled in the art would have recognized the disclosure as showing that the applicant was in possession of the claimed genus of protein variants at the time of filing.

Thus, Example 10 of the Guidelines teaches that the requirement for written description is satisfied where all variants are structurally similar to a particular sequence, *i.e.*, at least 95% identical.

Applicants respectfully submit that the scope of the claims include NBN polypeptides that are structurally similar to SEQ ID NO: 12 (*i.e.*, at least 95% identical), which further do not have substantial variation since all of the NBN polypeptides must possess a specified activity (*i.e.* neurotrophic activity). The specification provides multiple examples of these additional embodiments and teaches assays that would identify these structurally similar NBN polypeptides (*e.g.*, Examples 1-3). Additionally, the specification further describes conserved amino acids and motifs for certain embodiments, such as those recited in claims 81-83, thereby providing further evidence that the specification provides adequate written description of the subject matter now claimed.

Accordingly, applicants respectfully submit that the claims raise no issue written description.

***Reply to Claim Rejections Under 35 U.S.C. § 112, second ¶***

Claims 80-83 and 87-93 are rejected as allegedly being indefinite for recitation of the term “greater specificity”. Applicants respectfully disagree with this rejection. Nonetheless, claims 80 has been amended to remove “greater specificity” from the claims. Withdrawal of this rejection is respectfully requested.

**CONCLUSION**

An indication of allowance of all claims is respectfully solicited. Early notification of a favorable consideration is respectfully requested. In the event any issues remain, Applicant would appreciate the courtesy of a telephone call to their counsel to resolve such issues and place all claims in condition for allowance.

Respectfully submitted,

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